

### REMARKS

Claims 1, 2, 7-14, 24-27 and 38-44 are presently pending. Applicants gratefully acknowledge the Examiner's indication that claims 1, 2, 7-11, 13, 24 and 38 have been found to be allowable over the art of record.

Claims 14 and 25-27 have been withdrawn from consideration. Pursuant to a telephonic conference of May 10, 2004 with Examiner Richard Raymond, who has taken over examination of the above-identified application from Examiner John Ford, Applicants respectfully request rejoinder of method claims 14 and 25-27. Support for claims 14 and 25-27 in the present specification, as requested by Examiner Raymond, is set forth below (Section II).

Claim 12 has been amended to recite particular conditions which are responsive to IKK inhibition. Per a telephonic conference of May 25, 2004 with Examiner Raymond, Applicants respectfully request rejoinder of the following conditions which were withdrawn from consideration in the Office Action mailed December 24, 2002: an autoimmune condition, a cardiovascular condition, a metabolic condition, an ischemic condition, an infectious disease, stroke, epilepsy, Alzheimer's disease, Parkinson's disease and cancer. Support for the conditions recited in amended claim 12 is found in the specification as filed at page 17, lines 25-27 and claim 13 as filed (autoimmune condition); page 17, lines 28-30 and claim 15 as filed (cardiovascular, metabolic and ischemic conditions); page 17, lines 31-33 and claim 17 as filed (infectious diseases); page 18, lines 4-6 and claim 22 as filed (stroke, epilepsy, Alzheimer's disease and Parkinson's disease); and page 18, lines 1-3 and claim 20 as filed (cancer).

The link between the treatment of these conditions and the inhibition of IKK (*i.e.*, IKK-1 and IKK-2) is described in the specification as filed in the Background of the Invention. As set forth in the specification at page 1, line 13 to page 4, line 11, it is well known in the art that IKK inhibitors are useful for treating numerous conditions. IKK is a key regulatory signaling molecule that coordinates the activation of NF- $\kappa$ B. NF- $\kappa$ B is a key regulator of inflammatory gene transcription and is activated in the rheumatoid arthritis synovium (Aupperle et al. *J. Immunol.* 163:427-433, 1999). The expression of more than 70 known proteins is transcriptionally regulated by the binding of NF- $\kappa$ B to specific sequence elements in the promoter region of these genes (Baeuerle and Baichwal, *Advances in Immunology* 65:111 -137, 1997). Because of its role in regulating NF- $\kappa$ B, IKK has also been implicated in many pathophysiologic processes including angiogenesis (Koch et al., *Nature*

376:517-519, 1995), atherosclerosis (Brand et al., *J Clin Inv.* 97:1715-1722, 1996), endotoxic shock and sepsis (Bohrer et al., *J. Clin. Inv.* 100:972-985, 1997), inflammatory bowel disease (Panes et al., *Am J Physiol.* 269:H1955-H1964, 1995), ischemia/reperfusion injury (Zwacka et al., *Nature Medicine* 4:698-704, 1998), and allergic lung inflammation (Gosset et al., *Int Arch Allergy Immunol.* 106:69-77, 1995). Thus, because of nexus between the role of IKK and numerous conditions, inhibition of IKK is an art-accepted strategy for treating or preventing such conditions.

New claims 39-44 relating to methods for treating particular conditions responsive to IKK inhibition have been added.

Support for claim 39 reciting particular cardiovascular and metabolic conditions is found in the specification as filed at page 19, lines 10-18 and claim 16 as filed.

Support for claim 40 reciting a particular infectious disease is found in the specification as filed at page 19, lines 28-29 and claim 18 as filed.

Support for claim 41 reciting particular causes of the viral infections is found in the specification as filed at page 19, lines 28-31 and claim 19 as filed.

Support for claim 42 reciting particular cancers is found in the specification as filed at page 19, lines 23-25 and claim 21 as filed.

Support for claim 43 reciting combination therapy for the treatment of cancer is found in the specification as filed at page 20, lines 34-35 and page 21, line 30 and claim 23 as filed.

Support for claim 44 reciting particular additional anti-cancer agents is found in the specification as filed at page 21, line 30 to page 22, line 18 and claim 35 as filed.

No new matter has been added.

#### **I. Rejection of Claim 12 Under 35 U.S.C. § 112, First Paragraph**

Claim 12 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly not complying with the Utility Guidelines.

As the Examiner is aware, the PTO cannot reject a claim under 35 U.S.C. §112, first paragraph, for lack of utility unless it has reason to doubt the objective truth of the statements contained in the written description. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). And only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *In re Cotright*, 165 F.3d 1353, 1357 (Fed. Cir. 1999). Although no evidence has been provided by

the PTO regarding a lack of utility in connection with the presently claimed invention, Applicants respectfully point to the above discussion in the Remarks section regarding the sections of the specification which support (*i.e.*, demonstrate the link between the treatment of the claimed conditions and the inhibition of IKK) the utility of the presently claimed invention.

In view of the abundance of evidence provided showing the art's recognition of the usefulness of IKK-2 inhibitors for treating disease, Applicants respectfully submit that the PTO has a particularly high burden of showing that one of ordinary skill in the art would reasonably doubt the usefulness of the present anilino-pyrimidine derivatives for treating the recited conditions which are responsive to IKK-2 inhibition. *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980). Since the PTO has not met its burden, the rejection of claim 12 under 35 U.S.C. § 112, first paragraph, cannot stand and must be withdrawn.

## **II. Rejection of Claim 14 Under 35 U.S.C. § 112, First Paragraph**

Claim 14 has been withdrawn and stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly not claiming a reasonable number of uses.

As requested by Examiner Raymond during the telephonic conference of May 10, 2004, Applicants have respectfully requested rejoinder of claim 14.

Although there is no statutory basis for the rejection applied by the previous Examiner, Applicants respectfully submit that claim 14 sets forth a "reasonable number" of uses (*i.e.*, inflammatory conditions treatable by administration of an effective amount of a compound of claim 13 to a patient in need thereof). Support for the uses recited in claim 14 is found in the specification as filed at page 19, lines 10-20. And, as discussed above, there is an art accepted correlation between IKK activity and such conditions.

In view of the above remarks, Applicants believe the rejection of claim 14 under 35 U.S.C. § 112, first paragraph, cannot stand and must be withdrawn.

## **III. The Withdrawal of Claims 25-27**

Claims 25-27 have been withdrawn from consideration for allegedly not being of the same scope as claim 1 due to additional active ingredients.

As requested by Examiner Raymond during the telephonic conference of May 10, 2004, Applicants have respectfully requested rejoinder of claims 25-27.

Support for claim 25 is found in the specification as filed at page 21, line 17. Support for claim 26 is found in the specification as filed at page 21, lines 17-29. Support for claim 27 is found in the specification as filed at page 19, lines 10-20.

In view of the above remarks, Applicants believe that claims 25-27 are now in condition for allowance.

#### IV. Conclusion

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly requested. The Examiner is invited to call the undersigned with any questions concerning the foregoing.

It is believed that no fee is due other than that for the extension of time; however, in the event any other fee is required, please charge the required fee to Jones Day Deposit Account No. 503013.

Date May 27, 2004

Respectfully submitted,

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*Enclosures*